| Notice of Allowability | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/139,425 | ESMON ET AL. | |
| | Examiner | Art Unit | |
| | Sumesh Kaushal Ph.D. | 1636 | |

***-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--***

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *1/13/05*.

2. ☒ The allowed claim(s) is/are *1-13,15-18 and 22-25*.

3. ☒ The drawings filed on *09 August 1999* are accepted by the Examiner.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
**THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS ( as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review ( PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

**Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).**

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

**Attachment(s)**

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

Sumesh K.
SUMESH KAUSHAL
PATENT EXAMINER

## EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Steven Highlander on 03/28/05.

The application has been amended as follows:

**IN THE CLAIMS**

Claims 14 and 19-21 are canceled.

1. (currently amended) A method for selectively delivering a molecule to the nucleus of endothelial cells of large vessels, comprising

directly administering a conjugate to large vessel endothelial cells,

wherein the conjugate comprises an agent binding selectively to endothelial protein C receptor (EPCR) which causes uptake by the cell and transfer into the nucleus ~~conjugated to~~ of the molecule to be delivered,

wherein the conjugate is formed between the molecule to be delivered and an agent selected from the group consisting of activated protein C and an antibody to EPCR.

2. (original) The method of claim 1 wherein the conjugate is formed between the molecule to be delivered and an antibody to EPCR.

3. (original) The method of claim 1 wherein the conjugate is formed between the molecule to be delivered and activated protein C.

4. (original) The method of claim 1 wherein the conjugate comprises a chimeric antibody binding to the molecule to be delivered and to EPCR.

5. (currently amended) The method of claim 1 wherein the molecule to be delivered is a nucleic acid molecule, ~~and~~ wherein the nucleic acid molecule is a gene or cDNA under the control of a promoter expressed in the nucleus of an endothelial cell, ~~and~~ wherein the nucleic acid molecule is delivered by directly contacting the endothelial cells of large vessels with the nucleic acid molecule conjugate or by catheterization to the endothelial cells.

6. (original) The method of claim 5 wherein the nucleic acid molecule is selected from the group consisting of triplex forming oligonucleotides, ribozymes, guide sequences for ribozymes, and antisense.

7. (currently amended) The method of claim 1 wherein the molecule to be delivered is selected from the group consisting of drugs, proteins and diagnostic agents~~, wherein the drug is not a nucleic acid~~.

8. (original) The method of claim 1 wherein the molecule to be delivered is a protein.

9. (original) The method of claim 8 wherein the protein is a transcription factor.

10. (original) The method of claim 1 wherein the molecule to be delivered is coupled to the agent which binds to EPCR by molecules selected from the group consisting of streptavidin and biotin, and molecules having multiple positive charges.

11. (original) The method of claim 1 wherein the conjugate is administered to large vessel endothelial cells in culture or isolated from an individual.

12. (previously amended) The method of claim 1 wherein the conjugate is administered directly to an individual.

13. (currently amended) A conjugate comprising ~~of~~ an agent binding selectively to endothelial protein C receptor (EPCR) selected from the group consisting of ~~protein C,~~ activated protein C and antibodies reactive with EPCR, and a nucleic acid molecule to be delivered to a large vessel endothelial cell, ~~fragment of the antibodies reactive with EPCR binding to EPCR, and a molecule selected from the group consisting of nucleic acids, proteins, and drugs to be delivered to a large vessel endothelial cell, wherein the molecule is not a diagnostic label,~~ wherein the conjugate is a chemical conjugate, ~~fusion protein~~ or conjugate formed by indirect binding by a positively charged polymer, chimeric antibody or streptavidin.

14. (canceled)

15. (previously amended) The conjugate of claim 13 wherein the conjugate is formed between the ~~agent~~ nucleic acid molecule to be delivered and activated protein C.

16. (original) The conjugate of claim 13 wherein the molecule to be delivered is a nucleic acid molecule in combination for means for directly contacting the nucleic acid molecule conjugate directly with the endothelial cells of large vessels, wherein the means are for in vitro treatment of the cells or by catheterization to the endothelial cells.

17. (original) The conjugate of claim 16 wherein the nucleic acid molecule is a gene or cDNA under the control of a promoter expressed in the nucleus of an endothelial cell.

18. (original) The conjugate of claim 16 wherein the nucleic acid molecule is selected from the group consisting of triplex forming oligonucleotides, ribozymes, guide sequences for ribozymes, and antisense.

19. (canceled).

20. (canceled).

21. (canceled).

22. (currently amended) The conjugate of claim 13 ~~20~~ comprising coupling means which binds the nucleic acid molecule to be delivered to the agent which binds EPCR.

23. (original) The conjugate of claim 22 wherein the coupling means is a positively charged polymer or molecule.

24. (original) The conjugate of claim 22 wherein the coupling means is streptavidin-biotin

25. (currently amended) The conjugate of claim 13 comprising a chimeric antibody which binds to EPCR and to the nucleic acid molecule to be delivered.

## REASONS FOR ALLOWANCE

The following is an examiner's statement of reasons for allowance:

Claims 1-13, 15-18 and 22-25 are free of prior art of record because the prior art does not teach or suggest a method for selectively delivering a molecule to the nucleus of an endothelial cell of a large vessel by directly administering a conjugate comprising an activated protein C or an antibody to EPCR and a molecule to be delivered to large vessel endothelial cells, which causes uptake by the cell and transfer of the molecule to the nucleus of the cell. In addition the cited art does not teach of suggest a conjugate comprising an activated protein C or an antibody to EPCR and a nucleic acid molecule.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUMESH KAUSHAL
PATENT EXAMINER